PATENT SPECIFICATION

(11) **1 561 005**

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(21) Application No. 12923/77 (22) Filed 28 March 1977
(31) Convention Application Nos. 672 388 and 672 437
(32) Filed 31 March 1976 in
(33) United States of America (US)
(44) Complete Specification published 13 Feb. 1980
(51) INT CL³ C07D 473/28; A61K 31/52
(52) Index at acceptance
C2C 1422 1602 20Y 214 215 220 22Y 247 250 252 25Y 281 305 30Y 313 31Y 321 326 32Y 333 339 341 342 34Y 351 352 366 368 386 387 43X 601 620 626 628 62X 630 635 65X 66X 670 678 727 761 764 802 80Y AA KD KS LK LY TL

(19)

(54) XANTHINE COMPOUNDS AND METHOD OF TREATING BRONCHOSPASTIC AND ALLERGIC DISEASES

(71) We, COOPER LABORATORIES, INC. a C-- existing under the laws of the State of N-- Route 46, Parsi--

SPECIFICATION NO 1561005

By a direction given under Section 30 of the Patents Act 1977 this application proceeded in the name of BERLEX LABORATORIES, INC., a Corporation organised under the laws of the State of Delaware, United States of America, of 110 East Hanover Avenue, Cedar Knolls, New Jersey 07927, United States of America.

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THE PATENT OFFICE

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... they are sensitized. The antigen
... body of certain chemicals (allergic mediators) which in produce the allergic symptoms. Allergic reactions can also produce effects in organs other than the bronchi, particularly the skin, eyes and nasal mucosa and include such diseases as allergic rhinitis and urticaria.

Acute asthmatic bronchospasm has been treated with drugs which relax bronchial smooth muscle. Sympathomimetic drugs such as epinephrine, isoproterenol, and terbutaline and xanthine drugs such as theophylline and its salts (aminophylline, etc.) have been used for this purpose. Drugs such as cromolyn sodium which inhibit the release of allergic mediators, have been used prophylactically to treat bronchial asthma. Corticosteriod drugs have also been used to treat bronchial asthma and other allergy diseases.

Many of the drugs used hitherto have shortcomings which make them less than ideal for treatment of asthma and other bronchospastic and allergic diseases. For example, epinephrine and isoproterenol relieve the symptoms of asthma for only a relatively short period of time and are ineffective orally. Theophylline has limited efficacy and produces cardiac and gastrontestinal side effects. Cromolyn sodium is only effective by inhalation or injection and is ineffective by oral administration. The corticosteriod drugs have serious side effects which limit their chronic use.

Substituted xanthines have been known for some time as bronchodilators, and theophylline (1,3-dimethylxanthine) has long been used in the treatment of bronchial asthma.

Prior attempts have been made to improve theophylline by substituting the xanthine nucleus with different groups in several positions in the molecule. A number of 1,3-dialkylxanthines and 1,3,8-trialkylxanthines have been shown to be bronchodilators in animal models. However, none of the substituted xanthine compounds hitherto synthesized have displaced theophylline and its salts as clinically useful bronchodilator and antiallergy agents.

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(19)

(54) XANTHINE COMPOUNDS AND METHOD OF TREATING BRONCHOSPASTIC AND ALLERGIC DISEASES

(71) We, COOPER LABORATORIES, INC., a Company organised and existing under the laws of the State of New Jersey, United States of America, of 1259 Route 46, Parsipanny, New Jersey 07054, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to substituted xanthines which are useful in the treatment of bronchial asthma and other bronchospastic and allergic diseases. The invention also relates to pharmaceutical compositions comprising such a substituted xanthine and a pharmaceutically-acceptable carrier.

Bronchial asthma is characterized by bronchospasm caused by contraction of the bronchial smooth muscle, increased secretion of mucus from the bronchi, and edema of the respiratory mucosa. While the etiology of asthma is not completely known, it is believed to involve an allergic reaction. Allergic reactions occur in sensitized individuals who are exposed to the antigen to which they are sensitized. The antigen provokes the release in the body of certain chemicals (allergic mediators) which in turn produce the allergic symptoms. Allergic reactions can also produce effects in organs other than the bronchi, particularly the skin, eyes and nasal mucosa and include such diseases as allergic rhinitis and urticaria.

Acute asthmatic bronchospasm has been treated with drugs which relax bronchial smooth muscle. Sympathomimetic drugs such as epinephrine, isoproterenol, and terbutaline and xanthine drugs such as theophylline and its salts (aminophylline, etc.) have been used for this purpose. Drugs such as cromolyn sodium which inhibit the release of allergic mediators, have been used prophylactically to treat bronchial asthma. Corticosteriod drugs have also been used to treat bronchial asthma and other allergy diseases.

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Substituted xanthines have been known for some time as bronchodilators, and theophylline (1,3-dimethylxanthine) has long been used in the treatment of bronchial asthma.

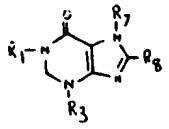
Prior attempts have been made to improve theophylline by substituting the xanthine nucleus with different groups in several positions in the molecule. A number of 1,3-dialkylxanthines and 1,3,8-trialkylxanthines have been shown to be bronchodilators in animal models. However, none of the substituted xanthine compounds hitherto synthesized have displaced theophylline and its salts as clinically useful bronchodilator and antiallergy agents.

A class of substituted xanthine compounds has now been found which are very

effective bronchodilator and antiallergy agents with rapid onset and prolonged duration of action. These compounds are effective, rapid-acting bronchodilators by all routes of administration and accordingly can be used to abort an acute bronchospastic attack. In addition, they are orally effective, long-acting antiallergy compounds, by suppressing the release of allergic mediators. Hence, these compounds may be used prophylactically to treat bronchial asthma, and other bronchospastic and allergic diseases.

As will be appreciated from the Examples which follow, the compounds of the invention may be used prophylactically as well as in acute bronchospastic and allergic attacks. It will also be appreciated that long-lasting relief of bronchial asthma and other bronchospastic and allergic disease may be achieved using compounds according to the invention.

According to this invention, there are provided novel xanthine compounds with which bronchial asthma and other bronchospastic and allergic diseases can be treated in mammals, the xanthine compounds having the general formula:



Formula I

wherein

$R_1 = C_1$—C_2 alkyl;

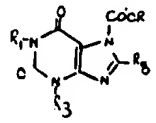
$R_3 = -CH_2-(C_3-C_4)$ alkyl or $-CH_2-(C_3-C_6$ cycloalkyl);

$R_7 = H$ or COOR in which $R = C_1$—C_4 alkyl, 2-halo C_2—C_3 alkyl or phenyl;

$R_8 = H$ or C_1—, alkyl; provided that R_7 and R_8 are not simultaneously H.

"Halo" as used herein means chloro or bromo.

The novel compounds of this invention which are preferred as bronchodilator and antiallergy agents have the following general formula:—



wherein:

$R_1 = C_1$—C_2 alkyl,

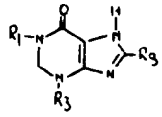
$R_3 = CH_2(C_3$—C_4 alkyl),

or $-CH_2-(C_3$—C_4 cycloalkyl),

$R_8 = C_1$—C_2 alkyl,

$R = C_1$—C_4 alkyl, 2-halo (C_2—C_3 alkyl), phenyl.

According to another preferred embodiment of this invention prolonged bronchodilation and prolonged inhibition of allergic mediator release in mammals are produced by administering an effective amount of a substituted xanthine compound having the formula:



wherein:

R_1 = methyl

$R_3 = -CH_2-(C_3$—C_4 alkyl); $-CH_2-(C_3$—C_4 cycloalkyl)

$R_8 = C_1$—C_2 alkyl

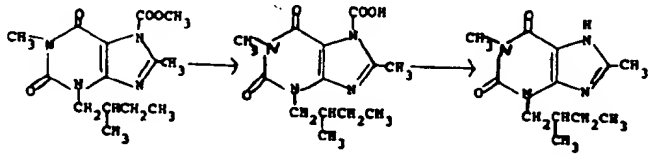
The compounds of the invention may be administered orally, parenterally, or by inhalation and conveniently will take the form of tablets, capsules, solutions, elixirs, emulsions or aerosols. Typical effective doses in man range from 0.01 to 50 milligrams per kilogram of body weight depending on route of administration and potency of compound selected.

R_3 may, for example, be *n*-butyl, *iso*-butyl, *n*-pentyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2,2-dimethyl-1-propyl, cyclopropylmethyl or cyclobutylmethyl.

R_1 may, for example be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 1-methylpropyl or t-butyl.

R may, for example be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 2-chloroethyl, 2-chloropropyl, 2-bromoethyl, 2-bromopropyl or phenyl.

The presence of a carboalkoxy group in the 7-position of the compounds of this invention has been found to give an improvement in efficacy and, as shown for example in Example 5 below, this effect is similar to the effect achieved in the case of prior art compounds (e.g. 7-carbomethoxy-theophylline as compared to theophylline itself). The data show that the xanthine carboxylate ester is more potent, with both faster onset and longer duration of action. These data indicate a greater bioavailability of the xanthine carboxylate ester. The 7-carboalkoxyxanthines are believed to act as latent forms of the alkylxanthine bronchodilators and are biotransformed to the corresponding xanthine-7-carboxylic acids, which then decarboxylate to yield the corresponding alkylxanthine. Thus for the case of 1,8 - dimethyl - 3 - (2 - methylbutyl) - xanthine - 7-carboxylic acid, methyl ester, the major reaction sequence is thought to proceed as follows:



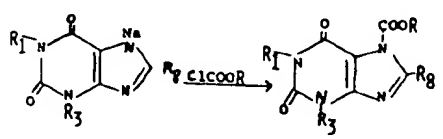
It is preferred to have R_8=methyl. The introduction of an alkyl group in the 8-position of the xanthine nucleus has been discovered to produce a compound having a long lasting activity. As shown below in Example 6, all of the 8-alkylxanthine bronchodilators have a longer duration of activity than the corresponding 8—H xanthine. It is believed that the 8-alkyl group prevents the normal enzymic oxidation at the 8-position of xanthines and thereby prevents rapid bioinactivation of the xanthine.

It is preferred to have R_3 selected from the following groups mentioned earlier, namely n-butyl, isobutyl, n-pentyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2,2-dimethyl-1-propyl, cyclopropylmethyl and cyclobutylmethyl. More preferred R_3 groups of those listed above are isobutyl, 2-methyl-1-butyl, 3-methyl-1-butyl, n-pentyl, 2,2-dimethyl-1-propyl, cyclopropylmethyl and cyclobutylmethyl groups. Of these, isobutyl and 2-methyl-1-butyl are especially preferred and 2-methyl-1-butyl is most preferred. This group has to the Applicant's knowledge never been reported as a substituent in a xanthine compound and has a significant advantage over the prior art R_3 groups. In comparison with the known R_3 groups, as shown below in Example 7, the 2-methyl-1-butyl group surprisingly confers on the xanthine bronchodilators an effectiveness equal to the best R_3 group reported in the prior art, the isobutyl group. This is surprising because the next higher homolog, the 2-methyl-1-pentyl group, confers much lower bronchodilation potency. Furthermore, the 2-methyl-1-butyl group surprisingly combines this great potency with a substantially lower toxicity. Thus the 2-methyl-1-butyl group is uniquely suitable for the R_3 group of a xanthine bronchodilator, particularly in combination with a 7-carboalkoxy group which, as previously indicated, increases the efficacy of the compound, and therefore such compounds which contain the 2-methyl-1-butyl group are greately preferred.

Thus the preferred groups for R_1, R_8 and R are methyl. The most preferred group for R_3 is 2-methyl-1-butyl. The most preferred compound is that which combines all four preferred groups, namely 1,8 - dimethyl - 3 - (2 - methyl - 1 - butyl) - 7-carbomethoxyxanthine.

A highly preferred compound is 1,8-dimethyl-3-isobutylxanthine. This compound has great potency and is long-acting. The most preferred compound wherein R_7=H is that which combines the preferred groups, namely 1,8-dimethyl-3-(2-methyl-1-butyl)xanthine. This compound has a unique combination of high potency, relatively low toxicity, and long-lasting activity.

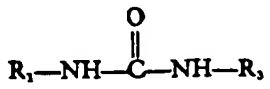
The 1,3,8-trialkyl-7-carboalkoxyxanthines of this invention may be prepared by reacting the sodium salt of the corresponding 1,3,8-trialkylxanthine with an alkyl chloroformate ClCOOR according to the following reaction:



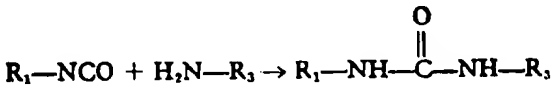
The sodium salt of the 1,3,8-trialkylxanthine can be prepared by the action of a strong base such as sodium hydride on the 1,3,8-trialkylxanthine. The reaction can be carried out in a suitable inert solvent such as tetrahydrofuran.

The 1,3,8-trialkylxanthines can be prepared by the well-known general procedure of Traube, Berichte *33*, 1371 and 3055 (1900).

A 1,3-dialkyl urea having the general formula



is first prepared. This urea can be prepared by reacting one mole of an alkyl isocyanate with one of an amine according to the reaction

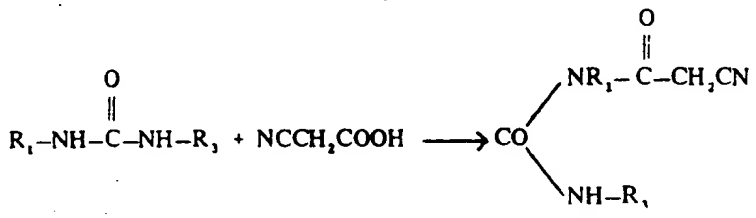


It is evident from the symmetry of the product that either R_1 or R_3 may be in the isocyanate reagent and either group may be in the amine reagent. The conditions under which this well-known reaction proceeds are known to one skilled in the art.

The isocyanate required for the above reaction may be prepared by reacting the corresponding amine with phosgene according to the equation

The conditions for this reaction are well known to those skilled in the art and are described in the chemical literature, e.g., in British Patent 901,337.

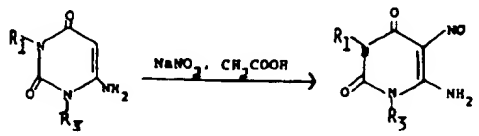
The 1,3-dialkyl urea is next converted into a 1,3-dialkyl-1-cyanoacetylurea by reaction with cyanoacetic acid according to the following reaction:



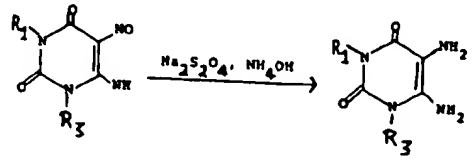
The reaction is conveniently carried out in acetic anhydride at 60° to 70°C. The reaction gives preferentially although not exclusively the product containing the smaller alkyl groups as R_1. The isomers may be separated by fractional crystallization. The 1,3-dialkyl-1-cyanoacetylurea is next cyclized to form a 4-amino-1,3-dialkyl-uracil according to the following reaction:

The reaction is carried out by treating the 1,3-dialkyl-1-cyanoacetylurea with a strong base such as sodium hydroxide in an aqueous medium.

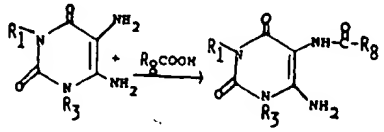
The 4-amino-1,3-dialkyl uracil is then converted into 4-amino-5-nitroso-1,3-dialkyluracil by treating with sodium nitrite in glacial acetic acid at room temperature, according to the following reaction:



The 4 - amino - 5 - nitroso - 1,3 - dialkyl - uracil is then reduced to a 4,5-diamino - 1,3 - dialkyluracil by reaction with sodium dithionite in ammonium hydroxide solution according to the following reaction:

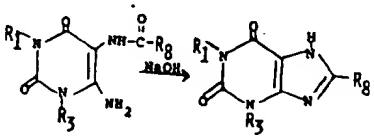


The 4,5-diamino-1,3-dialkyluracil is next converted to a 4-amino-5-alkanoylamino-1,3-dialkyluracil by reacting with a lower aliphatic acid according to the following equation:

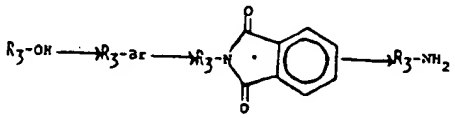


wherein R_8 is a lower alkyl group.

The 4-amino-5-alkanoylamino-1,3-dialkyluracil is then cyclized to form the 1,3,8-trialkylxanthine by heating in 10% aqueous sodium hydroxide solution to reflux temperature according to the following equation.



The compounds of this invention wherein R_3 contains an asymmetric carbon atom can exist in optically active enantiomeric forms. These forms may exist separately or mixed in any proportions. The racemic, or equimolar mixture of enantiomeric forms is obtained in the synthesis using reagents devoid of optical activity. The optically active forms of the substituted xanthines can be prepared by using the corresponding optically active amines R_3NH_2 in the synthesis. For example, the optically active dextro- or levo- form of the substituted xanthines having $R_3=CH_2CH(CH_3)CH_2\ CH_3$ can be obtained by starting with the corresponding optically active form of 2-methylbutylamine. Dextro- and levo-2-methylbutylamines can be prepared by from the corresponding commercially available dextro- and levo-2-methylbutanols by the procedure described by Vasi, I. G., and Desai, R. K., *J. Inst. Chemists Calcutta, 45*, 66 (1973).



The invention is to be understood as including within its scope processes, as described above, for preparing the novel compounds of the invention and, in its broad sense, this aspect of the invention is to be understood as being defined as follows:—

(A) A process for preparing a compound of Formula I in which R_7 is COOR which process comprises reacting a sodium salt of a 1,3-dialkyl- or 1,3,8-trialkylxanthine in which the 1-alkyl group is as defined for R_1 in Formula I, the 3-alkyl group is as defined for R_3 in Formula I and the 8-alkyl group is as defined for R_8 in Formula I, with an alkyl chloroformate of formula ClCOOR in which R is as defined in Claim 1.

(B) A process for preparing a compound of Formula I in which R_7 is hydrogen which process comprises cyclizing a 4-amino-5-alkanoylamino-1,3-dialkyluracil in which the 1-alkyl group is as defined for R_1 in Formula I, the 3-alkyl group is as defined for R_3 in Formula I and the alkanoylamino group is of formula $NHCOR_8$ in which R_8 is as defined for Formula I.

The compounds of this invention may be administered in the customary ways such as orally, sublingually, inhalation, rectally, and parenterally. Tablets, capsules, solutions, suspensions and aerosol mist may be used as forms for administration.

The compounds of this invention can be formulated into compressed tablets incorporating the customary inert excipients including diluents, binders, lubricants, disintegrants, colors, flavors, and sweetening agents. Commonly used pharmaceutical diluents such as calcium sulfate, lactose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar may be used.

Binders for tablets include starch, gelatin, sugars, such as sucrose, glucose, lactose, molasses, natural and synthetic gums such as acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, carboxymethyl cellulose and polyvinylpyrrolidone.

Commonly used lubricants for tablets include talc and hydrogenated vegetable oils, and these may used in compositions according to the invention in tablet form.

A disintegrant may if so desired be incorporated into the tablets. As disintegrants starches, clays, cellulose, algins, and gums may in particular be used as is well known to those skilled in the art.

Conventional coloring agents such as pharmaceutically acceptable dyes and lakes, and flavoring agents such as mannitol, lactose, or artificial sweetners may also be added to the tablet composition.

The compounds of this invention may also be administered orally contained in hard or soft capsules of gelatin or other suitable material. The compound of this invention may be present in the capsule alone or mixed with a suitable diluent such as lactose or starch.

The compounds of this invention may also be administered sublingually as rapidly disintegrating tablets or as troches or sublingual lozenges or pastilles. These dosage forms are prepared by mixing the active ingredient with flavored, rapidly dissolving or rapidly disintegrating excipients. For example a suitable base would comprise starch, lactose, sodium saccharin and talc.

Parenteral means can also be used for administering the compounds of this invention. They may be incorporated into implantable, slow-dissolving pellets or into aqueous injectable suspensions or solutions, or oily injectable media such as fixed oils. In general, the parenteral forms should be prepared just prior to use.

The compounds of this invention may also be administered by inhalation of a mist. The active compound may be dissolved or suspended in an aerosol propellant or suitable carrier liquid and loaded into a standard aerosol container with sufficient propellant to provide the proper pressure for dispensing the compound. These propellants are usually fluorinated or fluorochlorinated lower saturated aliphatic hydrocarbons. The active ingredient is then dispensed through a special valve in the form of a fine mist which is inhaled.

The great potency of 1,8 - dimethyl - 3 - (2 - methyl - 1 - butyl) - 7 - carbomethoxyxanthine and 1,8 - dimethyl - 3 - (2 - methyl - 1 - butyl)xanthine makes them preferred compounds for aerosol administration, like epinephrine and isoproterenol, to abort acute attacks. Aerosols of theophylline and its salts have been tried in the art, but the high doses required for these drugs to be efficacious and the resulting toxic reactions make this mode of administration impractical.

As is well-known in the pharmaceutical art, it is necessary in compounding dosage forms to avoid incompatibilities between ingredients. In formulating dosage forms containing the compounds of this invention, it is necessary to avoid combinations of ingredients which will result in the instability of the active compound if the dosage forms are to be stored for long periods of time. The particular incompatibilities to be avoided to attain this goal will be evident to one skilled in the art for each particular dosage form. Thus, for example, aqueous dosage forms of some of these compounds cannot be stored for long periods of time; however, they are perfectly satisfactory dosage forms if prepared immediately before administration.

It is preferred to administer the bronchodilator and antiallergy compounds of this invention orally in the form of tablets or capsules. Preferred dosage ranges in humans are from 2 to 50 mg. The following examples illustrate the practice of this invention but are not intended to limit its scope.

Example 1.

Synthesis of 1,8-dimethyl-3-(2-methyl-1-butyl) xanthine

Step 1

1-methyl-3-(2-methyl-1-butyl) urea (1)

$$CH_3NCO + H_2NCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HC_2H_5 \xrightarrow[100\%]{} CH_3NHCONHCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HC_2H_5$$

(1)

1.03 kg (11.8 mole) of 2-methyl-1-butylamine was added to 4.5 L of chloroform and the solution cooled to 0—5°C.

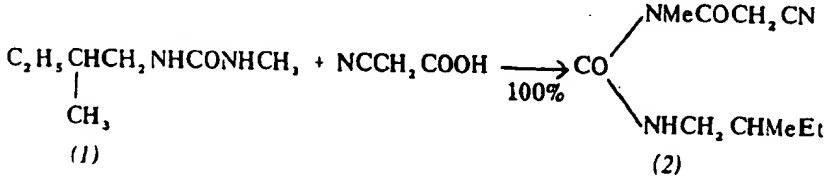
Then 674.0 g (11.8 mole) of methyl isocyanate was added slowly while maintaining the temperature at 0.5°C.

After the addition was complete the reaction was allowed to reach room temperature. Stirring was continued for 18 hours.

The chloroform was removed under vacuum to yield ~1.7 kg of 1-methyl-3-(2-methyl-1-butyl)urea *(1)* — an oil. Yield 100%.

Step 2

1-methyl-1-cyanoacetyl-3-(2-methyl-1-butyl) urea (2)



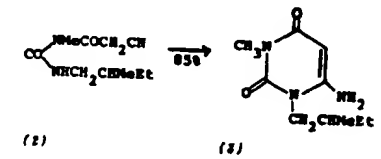
(1) *(2)*

To ~1.7 kg (11.8 mole) of 1-methyl-3-(2-methyl-1-butyl)urea *(1)* were added 4.3 L of acetic anhydride and 1.18 kg (13.9 mole) of cyanoacetic acid. This was heated for 2 hr. @ 60—70°C.

The acetic anhydride was removed under vacuum to yield ~2.9 kg of an oil. This material is a mixture of cyano acetic acid and 1-methyl-1-cyanoacetyl-3-(2-methyl-1-butyl)urea *(2)*. No attempt was made at purification; *(2)* was used immediately in the next step.

Step 3

4-amino-1-methyl-3-(2-methyl-1-butyl) uracil (3)



(2) *(3)*

10.3 L of 10% NaOH solution was slowly added to 2.9 kg (11.8 mole) of crude 1-methyl-1-cyanoacetyl-3-(2-methyl-1-butyl) urea *(2)* with stirring.

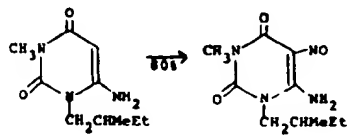
The oil dissolved and shortly another oil precipitated. The temperature rose to ~60°C and then dropped.

After stirring for a while at room temperature the oil crystallized.

After cooling the product was filtered. The crude product was slurried in water and dried @ 50°C *in vacuo* to yield ~2.1 kg of 4-amino-1-methyl-3-(2-methyl-1-butyl) uracil *(3)* (m.p. 121—124°C). Yield 85% from *(1)*.

Step 4

4-amino-5-nitroso-1-methyl-3-(2-methyl-1-butyl) uracil (4)



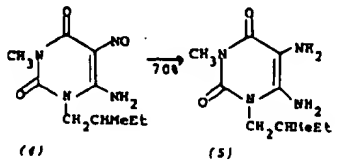
(3) *(4)*

21 kg (9.9 mole) of 4-amino-1-methyl-3-(2-methyl-1-butyl)uracil *(3)* was suspended in 22.0 L of water. A solution of 745.5 g (10.8 mole) of sodium nitrite in 5.7 L of water was added to the suspension. Then 1.2 L of glacial acetic acid was added dropwise and the suspension was stirred for 18 hr. at room temperature.

After cooling the precipitate was filtered. The crude product was slurried in water and dried @ 80° C *in vacuo* to yield ~1.9 kg of 4-amino-5-nitroso-1-methyl-3-(2-methyl-1-butyl)uracil *(4)* (m.p. 202—204°C). Yield 80%.

Step 5

4,5-diamino-1-methyl-3-(2-methyl-1-butyl) uracil (5)



8.65 L of conc. ammonium hydroxide (58%) was added to 1.9 kg (7.9 mole) of 4-amino-5-nitroso-1-methyl-3-(2-methyl-1-butyl)uracil *(4)*. An orange salt formed.

The suspension was placed in an oil bath at 80—90°C and a solution resulted.

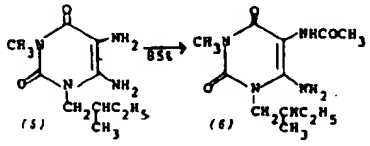
5.6 kg (32.3 mole) of sodium dithionite was added in portions over about 30 min. When the addition was complete stirring was continued for 30 min.

The reaction was allowed to cool to room temperature and stirred overnight.

After cooling the precipitate was filtered, slurried with water and dried @ 80°C *in vacuo* to yield ~1.25 kg of 4,5-diamino-1-methyl-3-(2-methyl-1-butyl)uracil *(5)* (m.p. 161—163°C). Yield 70%.

Step 6

4-amino-5-acetylamino-1-methyl-3-(2-methyl-1-butyl) uracil (6)

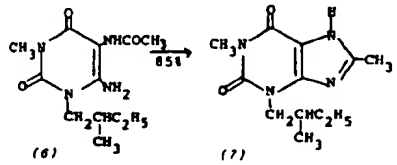


1.25 kg (5.5 mole) of 4,5-diamino-1-methyl-3-(2-methyl-1-butyl)uracil *(5)* was added to 4.5 L of glacial acetic acid and heated to reflux for 2 hrs.

The acetic acid was evaporated and the residue triturated with ether. The solid was filtered and dried @ 60°C *in vacuo* to yield ~1.26 kg. of 4-amino-5-acetylamino-1-methyl-3-(2-methyl-1-butyl)uracil *(6)* (m.p. 178—182°C). Yield 85%.

Step 7

1,8-dimethyl-3-(2-methyl-1-butyl) xanthine (7)



1.26 kg (4.7 mole) of 4-amino-5-acetylamino-1-methyl-3-(2-methyl-1-butyl)-uracil *(6)* was added to 3.9 L of 10% sodium hydroxide solution and heated at reflux for 30 min.

The solution was filtered and the filtrate cooled to room temperature.

The pH of the filtrate was adjusted to 5.0 with glacial acetic acid.

After cooling the precipitate was filtered. The crude product was slurried twice with water and dried @ 80°C *in vacuo* to yield about 1.0 kg of 1,8-dimethyl-3-(2-methyl-1-butyl)xanthine *(7)* (m.p. 189—191°C). Yield 85%.

Example 2.

1,3-dialkylxanthines and 1,3,8-trialkylxanthines

By the procedure of Example 1 a number of 1,3-dialkylxanthines and 1,3,8-trialkylxanthines are synthesized. By proper choice of the reagents containing the precursors of the R_1, R_3 and R_8 groups the particular compounds are synthesized. R_1 and R_3 are determined by the reagents reacted in Step 1, R_8 is determined by the carboxylic acid reagent used in Step 5. Table 1 shows the reagents used in Steps 1 and 5 to introduce R_1, R_3, and R_8, and produce the listed compound.

TABLE 1

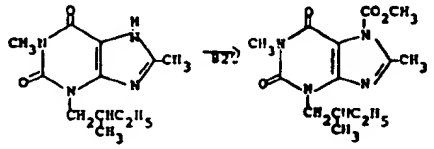
No.	Compound	STEP 1		STEP 5
		isocyanate	amine	acid
4315	1-methyl-3-(n-butyl)-xanthine	methyl isocyanate	n-butylamine	formic acid
4258	1-methyl-3-(isobutyl) xanthine	methyl isocyanate	isobutylamine	formic acid
6806	1-methyl-3-(n-pentyl) xanthine	methyl isocyanate	pentylamine	formic acid
4280	DL-1-methyl-3-(2-methyl-1-butyl)-xanthine	methyl siocyanate	2-methylbutyl-amine	formic acid
4340	1-methyl-3-(2,2-dimethyl-1-propyl) xanthine	methyl isocyanate	2,2-dimethyl-propylamine	formic acid
6840	1,8-dimethyl-3-(n-butyl)-xanthine	methyl isocyanate	n-butylamine	acetic acid
4506	1,8-dimethyl-3-n-pentyl-xanthine	methyl isocyanate	pentylamine	acetic acid
4500	1,8-dimethyl-3-isopentyl-xanthine	methyl isocyanate	isopentylamine	acetic acid
6738	1,8-dimethyl-3-(2,2-dimethyl-propyl)-xanthine	methyl isocyanate	neopentylamine	acetic acid
6796	D-1,8-dimethyl-3-(2-methyl-1-butyl) xanthine	methyl isocyanate	D-2-methyl-1-butylamine	acetic acid
6807	L-1,8-dimethyl-3-(2-methyl-1-butyl) xanthine	methyl isocyanate	L-2-methyl-1-butylamine	acetic acid
4490	DL-1-methyl-3-(2-methyl-1-butyl)-8-ethyl-xanthine	methyl isocyanate	2-methyl-1-butylamine	propionic acid
4489	DL-1-ethyl-3-(2-methyl-butyl-8-methyl-xanthine	ethyl isocyanate	2-methyl-1-butylamine	acetic acid

TABLE 1 (Continued)

No.	Compound	STEP 1		STEP 5
		isocyanate	amine	acid
4495	DL-1,8-diethyl-3-(2-methyl-1-butyl) xanthine	ethyl isocyanate	2-methyl-1-butylamine	propionic acid
4388	1,8-dimethyl-3-isobutyl-xanthine	methyl isocyanate	isobutylamine	acetic acid

Example 3.

1,8-dimethyl-3-(2-methyl-1-butyl) xanthine-7-carboxylic acid, methyl ester



1.0 kg (4.0 mole) of 1,8-dimethyl-3-(2-methyl-1-butyl)xanthine was suspended in 19.0 L of dry tetrahydrofuran.

288.0 g of sodium hydride (50% in oil) (6.0 mole) was washed with anhydrous ether and was then carefully added to the suspension.

The suspension was stirred for 1 hr. (a solution resulted).

567.0 g (4.0 mole) of methyl chloroformate was slowly added.

After addition was complete the reaction was heated to reflux for 18 hrs.

Then the reaction was filtered hot. The filtrate was evaporated and the residue triturated with hexane. The resultant solid was washed with a little ether, filtered and dried @ 40°C *in vacuo* to yield ~1.0 kg of 1,8-dimethyl-3-(2-methyl-1-butyl)-xanthine-7-carboxylic acid, methyl ester (m.p. 110—112°C). Yield 82%.

Example 4.

1,3-dialkylxanthine- and 1,3,8-trialkylxanthine-7-carboxylic acid esters

By the procedure of Example 3 using the corresponding 1,3,8-trialkylxanthine and ester of chloroformic acid listed in Table 2, the 1,3-dialkylxanthine- and 1,3,8-trialkyl-xanthine-7-carboxylic acid esters listed in Table 2 are prepared.

TABLE 2

No.	Product	Reagents	
		Xanthine	Chloroformic Ester
6896	1-methyl-3-(n-butyl)-xanthine-7-carboxylic acid, methyl ester	1-methyl-3-(n-butyl)-xanthine	methylchloroformate
4274	1-methyl-3-(isobutyl) xanthine-7-carboxylic acid, methyl ester	1-methyl-3-(isobutyl)-xanthine	methylchloroformate
6865	1-methyl-3-(n-pentyl) xanthine-7-carboxylic acid, methyl ester	1-methyl-3-(n-pentyl)-xanthine	methylchloroformate
4380	1-methyl-3-(2-methyl-1-butyl)xanthine-7-carboxylic acid, methyl ester	1-methyl-3-(2-methyl-1-butyl) xanthine	methylchloroformate
6854	1-methyl-3-(2,2-dimethyl-1-propyl) xanthine-7-carboxylic acid, methyl ester	1-methyl-3-(2,2-dimethyl-1-propyl) xanthine	methylchloroformate
6892	1,8-dimethyl-3-(n-butyl)-xanthine-7-carboxylic acid, methyl ester	1,8-dimethyl-3-(n-butyl) xanthine	methylchloroformate
4507	1,8-dimethyl-3-n-pentylxanthine-7-carboxylic acid, methyl ester	1,8-dimethyl-3-n-pentylxanthine	methylchloroformate
4505	1,8-dimethyl-3-iso-pentyl-xanthine-7-carboxylic acid, methyl ester	1,8-dimethyl-3-isopentylxanthine	methylchloroformate
6897	1.8-dimethyl-3-(2,2-dimethylpropyl) xanthine 7-carboxylic acid, methyl ester	1,8-dimethyl-3-(2,2-dimethyl propyl) xanthine	methylchloroformate
4390	1,8-dimethyl-3-iso-butylxanthine-7-carboxylic acid, methyl ester	1,8-dimethyl-3-isobutylxanthine	methylchloroformate
6919	D-1,8-dimethyl-3-(2-methyl-1-butyl)xanthine 7-carboxylic acid, methyl ester	D-1,8-dimethyl-3-(2-methyl-1-butyl)-xanthine	methylchloroformate

TABLE 2 (Continued)

No.	Product	Reagents	
		Xanthine	Chloroformic Ester
6938	L-1,8-dimethyl-3-(2-methyl-1-butyl)xanthine-7-carboxylic acid, methyl ester	L-1,8-dimethyl-3-(2-methyl-1-butyl)-xanthine	methylchloroformate
4491	DL-1-methyl-3-(2-methyl-1-butyl)-8-ethyl-xanthine-7-carboxylic acid, methyl ester	DL-1-methyl-3-(2-methyl-1-butyl)-8-ethylxanthine	methylchloroformate
4494	DL-1-ethyl-3-(2-methyl-1-butyl)-8-methyl-xanthine-7-carboxylic acid, methyl ester	DL-1-ethyl-3-(2-methyl-butyl)-8-methylxanthine	methylchloroformate
4498	DL-1,8-diethyl-3-(2-methyl-1-butyl)xanthine-7-carboxylic acid, methyl ester	DL-1,8-diethyl-3-(2-methyl-1-butyl)-xanthine	methylchloroformate
4477	DL-1,8-dimethyl-3-(2-methyl-1-butyl)xanthine ethyl ester	DL-1,8-dimethyl-3-(2-methyl-1-butyl) xanthine	ethyl chloroformate
4488	DL-1,8-dimethyl-3-(2-methyl-1-butyl)xanthine-7-carboxylic acid, n-propyl ester	DL-1,8-dimethyl-3-(2-methyl-1-butyl) xanthine	n-propyl chloroformate
6852	DL-1,8-dimethyl-3-(2-methyl-1-butyl)xanthine-7-carboxylic acid, 2-chloroethyl ester	DL-1,8-dimethyl-3-(2-methyl-1-butyl)-xanthine	2-chloroethylchloro-formate
6860	DL-1,8-dimethyl-3-(2-methyl-1-butyl)xanthine-7-carboxylic acid, phenyl ester	DL-1,8-dimethyl-3-(2-methyl-1-butyl)-xanthine	phenylchloroformate

In the following comparative examples results of pharmacological tests with a number of the compounds of this invention and of the prior art are presented. The pharmacological properties were evaluated by standard tests which are defined, together with the symbols used as follows:

BD Bronchodilator activity evaluated against histamine-induced bronchoconstriction in the guinea pig, and expressed as % protection at the stated time interval (in minutes and hours) post-drug against histamine agonist. Doses are expressed in milligrams per kilogram or body weight (mpk) *per os* (*po*) or intraperitoneally (*ip*).

A modification of the method of Siegmund. O. H., et. al., J. Pharmacol. and Exp. Therap. *90*:254—9, 1947, is used. Healthy guinea pigs weighing from 250 to 300 grams are placed four at a time and separated by wiring screening in an 11 liter plastic [illegible] at the time of peak activity following drug administration. The challenge

consists of histamine diphosphate (1% solution) aerosolized in a de Vilbiss #40 nebulizer at 200 mg Hg. ("de Vilbiss" is a Registered Trade Mark). Times for prostration are recorded. All animals exposed to the aerosols f r 10 minutes r longer without prostration, are arbitrarily considered fully protected.

Per cent protection is calculated as follows:

$$\% \text{ Protection} = \frac{100 \text{ (Test prostration time-control prostration time)}}{600 - \text{control prostration time}}$$

wherein the times are measured in seconds.

CP Cardiopulmonary activity evaluated against histamine-induced bronchoconstriction in the dog and expressed as % increase (↑) or decrease (↓) in the following parameters:

BP blood pressure
HR heart rate
PR pulmonary resistance
PC pulmonary compliance
RMV respiratory minute volume

The method used is that of Giles, R. E., Finkel, N. P., and Mazurowski, J., *Arch. Int. Pharmacodyn. Therap. 194,* 213 (1971). A simulated asthmatic state is induced in anesthetized spontaneously breathing dogs by graded intravenous doses of histamine. The degree of induced bronchoconstriction is reflected by proportionate increases in pulmonary resistance. Pretreatment with bronchodialtor drugs aims to block the bronchospastic response to histamine. Each dog serves as its own control. Mean values 2 hours post drug are given.

SP Spasmolytic activity evaluated *in vitro* using guinea pig tracheal chain prepartion, and expressed as the molar (M) concentration required to produce maximum relaxation.

The method used is that of Castillo and de Beer, *J. Pharmac. Expt. Therap. 90,* 104, 1947.

AA Antiallergy (anti-anaphylactic) activity evaluated against antigen-induced bronchoconstriction in rats sensitized with *N. brasliensis,* and expressed as % protection (R).

The method used is that of Church, N. K., Collier, H. O. J., and James, G. W. L., *Brit. J. Pharmacol. 46,* 56—65 (1972).

Rats sensitized with antigen from *Nippostrongylus brasiliensis* exhibit anaphylactic shock when re-exposed to this antigen 28 days later. The animals are subdivided into control and test groups.

Test animals receive a drug either orally, intraperitoneally or intravenously and are challenged with intravenous antigen at fixed time intervals after dosing. Antigen-induced increases in tracheal pressure are monitored and reflect the extent of bronchoconstriction.

PCA Antinaphthylactic activity against passive cutaneous anaphylaxis in the rat, expressed as % protection against antigen-induced wheal formation.

The method used is that of Ogilvie, B. M., *Immunology 12,* 113—131 (1967). Reaginic AgE antibodies develope in the rat following subcutaneous injection of Nippostrongylus brasiliensis larvae. Antisera, collected 28 days later are injected subcutaneously into new rats. These new rats when challenged with antigen 24 hours later exhibit an immediate type I reaction characterized by local swelling and edema (wheal) at the site of antisera injection.

LD_{50} Dose required to cause death of 50% of test animals.

The LD_{50} was determined in three species, the mouse (male 18—25 g), the albino rat (female, 150—200 g) and the albino guinea pig (male, 180—280 g) by oral administration and in the albino rat by intraperitoneal administration. The animals are fasted overnight prior to testing. Six groups of ten animals are used; five groups are dosed with the test substance, the sixth group serves as a control and receives the drug vehicle at the highest test concentration. The compounds were administered in a 0.5% gum tragacanth solution in distilled water using a constant logarithmic increment dose. Dose volume ranged from 5 to 40 mg/kg.

The animals were housed five per cage (rat and guinea pig) or ten per cage (mouse) with free access to food and water. The number of dead animals was recorded

daily for five consecutive days. The total mortality per group of ten for each dose level was recorded and LD_{50} with Confidence Limits calculated according to the method described by Weil, C. S., Biometrics 8(3): 249—263, 1952.

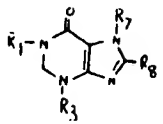
Example 5.

This Example illustrates the superiority of 7-carboalkoxyxanthines over the corresponding 7—H xanthines. Several pairs of compounds were tested in a number of assays as described above.

The results may be seen in Table 4 wherein corresponding xanthines with and without the 7-carbomethoxy group are compared, it being noted that some of the compounds appearing in the Table are known and included for comparison only. The effect can be seen most clearly by comparing the potency of the compounds in the bronchodilation assay in the guinea pig (BD[guinea pig]).

In interpreting the BD data it should be noted that a dose giving less than 40—50% protection is not considered useful. Differences in percent protection of less than 10% are probably not significant. 4378 gives 96% protection at 1 hour at a dose of 60 mpK while the corresponding compound devoid of the 7-carbomethoxy groups, 4296, gives only 53% protection at the larger dose of 100 mpK. Clearly, the 7-carbomethoxy derivative is superior. 4274 gives greater protection than 4258 at equal doses. In comparing 4387 and 4383 at equal doses (10 mpK) it can be seen that the 7-carbomethoxy compound 4387 shows greater activity. Although both of these compounds are already very potent, the benefit of the 7-carbomethoxy group is particularly evident in the dog at 1 mpK. Another comparison shows that 4260 is clearly superior to theophylline at the same dose (80 mpK).

TABLE 3 EFFECT OF 7-CARBOMETHOXY GROUP ON POTENCY



CPD.	R_1	R_3	R_8	R_7	BD *(guinea pig)* mpK 30′ 1h 2h 4h 6h 10h	AA *(rat)* mpK 1h	SP *(in vitro)* C	LD_{50} mpK spec
4296 *	CH_3	CH_3	CH_3	H	100po 53 45 43 23 150po 68 80 71 79 86 85	75ip 49	M/14	
4378 *	CH_3	CH_3	CH_3	$COOCH_3$	60po 96 95 89	75ip 54	M/10	
4258 *	CH_3	CH_2CHMe_2	H	H	15po 45 75 39 25po lethal 2/4	1.5ip 79 2.0ip tox	M/1000	
4274	CH_3	CH_2CHMe_2	H	$COOCH_3$	15po 92 87 64 18 40po lethal 1/6	5ip 74	M/2000	
4383	CH_3	$CH_2CHMeEt$	CH_3	H	10po 35 63 66 20po 92 100 97	2.5po 58	M/1000	21.7po g.pig 24.6ip rat 88.7po rat 60.6po mouse
4387	CH_3	$CH_2CHMeEt$	CH_3	$COOCH_3$	10po 44 87 59 37 20po 94 92	2.5po 72 5po 68 10po 57 5ip 55	M/1000	27.4po g.pig 54.9po mouse 18.3ip rat 60.0po rat
Theo-phylline	CH_3	CH_3	H	H	80po 32 69 42 17 100po 45 58 36 25 14	75ip 70 25po 50 100po 73	M/10	183po g.pig 225po rat 150ip rat
4260 *	CH_3	CH_3	H	$COOCH_3$	80po 99 100 86 95 0	75ip 82	M/20	

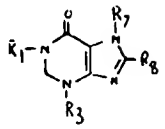
* for comparison.

Example 6.

This Example illustrates the prolonged activity of the 8-alkylxanthines over that of the corresponding 8—H compounds. The increased and prolonged activity of the 1,3,8-trialkyl-7-carboalkoxyxanthines relative to that of the 1,3-dialkyl-7-carboalkoxyxanthines may be seen in Table 4 which compares the activity of corresponding pairs of substituted xanthines with and without 8-alkyl groups, it again being noted that known xanthine compounds appear in the Table for comparative purposes.

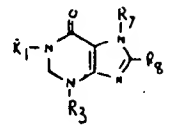
The data on bronchodilator activity in the guinea pig (BD[guinea pig]) show the prolonged activity of the compounds having an 8-alkyl group. In each pair the protection at 4 hours or 6 hours produced by the 8-methyl compound is greater than the protection by the corresponding compound devoid of the 8-methyl group. For pairs 4387 vs. 4380, 4390 vs. 4274, 4378 vs. 4260, pairs 4383 vs. 4280, 4388 vs. 4258 and 4296 vs. theophylline the 8-methyl derivatives are shown to be effective at lower doses and for longer duration than the 8—H compounds. This phenomenon is attributed to the 8-alkyl substituted interfering with the normal bioinactivation of 1,3-dialkylxanthines by enzymatic oxidation at the 8-position, and was not anticipated by the teachings of the prior art on xanthine compounds.

TABLE 4 PROLONGED ACTIVITY OF 8-ALKYLXANTHINES



Cpd.	R_1	R_3	R_8	R_7	BD *(guinea pig)* mpK	30′	1h	2h	4h	6h	10h	AA *(rat)* mpK	1h	SP *in vitro* C	LD_{50} mpK	spec.
4274	CH_3	CH_2CHMe_2	H	$COOCH_3$	15po	92	87	64	18			5ip	74	M/2000		
					40po	lethal 1/6										
4390	CH_3	CH_2CHMe_2	CH_3	$COOCH_3$	10po	49	86			79	48	2ip	60	M/1000	25.2po	g. pig
												4ip	52		27.6po	mouse
												2.5po	77		9.1ip	rat
															33.5po	rat
4260 *	CH_3	CH_3	H	$COOCH_3$	80po	99	100	86	95	0		75ip	82	M/20		
4378 *	CH_3	CH_3	CH_3	$COOCH_3$	60po		96		95	89		75ip	54	M/10		
4380	CH_3	$CH_2CHMeEt$	H	$COOCH_3$	40po		99		57	12		5po	66	M/700		
					20po		64									
4387	CH_3	$CH_2CHMeEt$	CH_3	$COOCH_3$	10po	44	87			59	37			M/1000	27.4po	g. pig
					20po		94			92		2.5po	72		54.9po	mouse
												5po	68			
												10po	57		18.3ip	rat
															60.0po	rat

TABLE 4 PROLONGED ACTIVITY OF 8-ALKYLXANTHINES



Cpd.	R_1	R_3	R_8	R_7	BD *(guinea pig)* mpK 30′ 1h 2h 4h 6h 8h	AA *(rat)* mpK 1h	SP *in vitro* C	LD_{50} mpK spec.
4280 *	CH_3	$CH_2CHMeEt$	H	H	20po 86 86 80 13 80po lethal 3/8	15ip 56	M 1000	
4383	CH_3	$CH_2CHMeEt$	CH_3	H	10po 35 63 66 20po 92 100 97	2½po 58 4ip 57	M 1000	21.7po g. pig 24.6ip rat 88.7po rat 66.6po mouse
4258 *	CH_3	CH_2CHMe_2	H	H	15po 45 75 39 25po lethal 2/4	1.5ip 79 2.0ip tox	M 1000	
4388	CH_3	CH_2CHMe_2	CH_3	H	10po 76 73 80 20po lethal 1/4	2.5po 50	M 1000	
Theo-phylline	CH_3	CH_3	H	H	80po 32 69 42 17 100po 45 58 36 25 14	75ip 70 225po 50 100po 73	M 10	183po g. pig 225po rat 150ip rat
4296 *	CH_3	CH_3	CH_3	H	100po 53 45 43 23 150po 68 80 71 79 86 85	75ip 49	M. 14	

* for comparison.

Example 7.

This Example illustrates, in some instances by reference to known compounds for comparison, the decreased toxicity of substituted xanthines having R_3 = 2-methyl-1-butyl over those having R_3 = isobutyl while the potency of the compounds remains approximately equal.

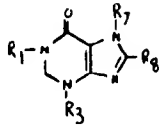
The unexpected improvement in activity of 1-alkyl-3-(2-methyl-1-butyl)-7-carbomethoxy xanthines, without a corresponding increase in toxicity with reference to the corresponding 3-isobutyl homologs can be seen in Table 5 where the data for corresponding pairs of compounds is presented. This effect is seen most clearly in the pair 4387 vs. 4390. The effectiveness of the 7-carbomethoxy compounds can be compared in the bronchodilation assay in the guinea pig and the antiallergy assay in the rat. The effectiveness data show that the 1-methyl-3-(2-methyl-1-butyl)-8-methyl-7-carbomethoxyxanthines (4387) is about as effective as the corresponding 3-isobutyl compound (4390) in the guinea pig, rat and dog assays. Yet 4387 is only about one-half as lethal as 4390 in the rat and mouse. Likewise, in the guinea pig toxic effects can be seen in the case of the xanthines having the 3-isobutyl group, while at the same dose the corresponding compound having the 3-(2-methyl-1-butyl) group is effective and non-toxic.

Among the 1,3,8-trialkylxanthines, 4383 has about the same bronchodilation potency as 4388 in the BD (guinea pig) assay at a dose of 10 mpK *per os*; yet at a dose of 20 mpK *po* 4383 shows no toxic effects while 4388 shows pronounced toxicity and was even lethal to one animal.

4280 and 4258 show about equal potency as shown by the results for doses of 20 mpK *po* and 15 mpK *po* respectively; however 4258 shows lethal effects at only 25 mpK *po* while 4280 must be given at a dose of 80 mpK *po* to show similar lethal effects.

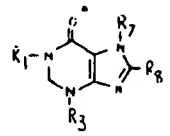
Clearly, the xanthines having a 2-methyl-1-butyl group in the 3-position are less toxic than those having a 3-isobutyl group.

TABLE 5 EQUAL ACTIVITY WITHOUT INCREASED TOXICITY
3-(2-METHYLBUTYL) VS. 3-ISOBUTYL



Cpd.	R_1	R_3	R_8	R_7	BD *(guinea pig)* mpK	30′	1h	2h	4h	6h	10h	AA *(rat)* mpK	1h	SP *in vitro* C	LD_{50} mpK	spec.
4390	CH_3	CH_2CHMe_2	CH_3	$COOCH_3$	10po	49	86			79	48	2ip	60	M/1000	25.2po	g. pig
					20po	lethal 1/2						4ip	52		27.6po	mouse
															9.1ip	rat
												2.5po	77		33.5po	rat
4387	CH_3	$CH_2CHMeEt$	CH_3	$COOCH_3$	10po	44	87			59	37			M/1000	27.4po	g. pig
					20po		94			92		2.5po	72		54.9po	mouse
												5po	68			
												10po	57			
												5ip	55		18.3 ip	rat
															60.0po	rat
4274	CH_3	CH_2CHMe_2	H	$COOCH_3$	15po	92	87	64	18			5ip	74	M/2000		
					40po	lethal 1/6										
4380	CH_3	$CH_2CHMeEt$	H	$COOCH_3$	40po		99			57	12	5po	66	M/700		
					20po		64									

TABLE 5 EQUAL ACTIVITY WITHOUT INCREASED TOXICITY
3-(2-METHYLBUTYL VS. 3-ISOBUTYL)



	R_1	R_3	R_8	R_7	BD *(guinea pig)* mpK 30′ 1h 2h 4h 6h 8h	AA *(rat)* mpK 1 1h	SP *in vitro* C	LD_{50} mpK spec.
4388	CH_3	CH_2CHMe_2	CH_3	H	10po 76 73 80 20po lethal 1/4	2.5po 50	M/1000	
4383	CH_3	$CH_2CHMeEt$	CH_3	H	10po 35 63 66 20po 92 100 97	2.5po 58	M/1000	21.7po g. pig 24.6ip rat 88.7po rat 66.6po mouse
4258 *	CH_3	CH_2CHMe_2	H	H	15po 45 75 39 25po lethal 2/4	1.5ip 79 2.0ip tox	M/1000	
4280 *	CH_3	$CH_2CHMeEt$	H	H	20po 86 86 80 13 80po lethal 3/8	15ip 56	M/1000	

* for comparison.

Example 8.

This Example illustrates (again with reference to known xanthines) the activity of substituted xanthines according t this invention and the variation in pharmacological effects produced by introducing different R_3 substituents.

Table 6 shows the results of the bronchodilation assay described above in the guinea pig for a series of 1,3-dialkyl and 1,3,8-trialkylxanthine-7-carboxylates in which the R_3 group was varied. The most effective compounds are those in which the lowest dose produces an acceptable bronchodilation (~40%). Data is also included showing effectiveness in the antiallergy assay in the rat, and the *in vitro* bronchodilation activity.

The data for the effectiveness of the compounds shown in the Table 6 teaches that the activity of xanthine bronchodilators depends not only upon the total number of carbon atoms comprising R_1, R_3, R_8 and R, but also upon the distribution of these carbon atoms among R_1, R_3, R_8 and R, and especially upon the branching within the structure of the R_3 group.

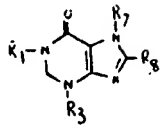
Maximum activity is obtained when $R_1 = R_8 = R =$ methyl and R_3 is a C_4 or C_5 alkyl group. Peak activity is obtained when the alkyl group of R_3 is branched at the number 2 carbon

$$-CH_2CHR$$
$$\quad\;\;|$$
$$\quad CH_3$$

as in 2-methyl-1-butyl.

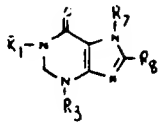
Optimal activity, i.e., maximum activity with relatively lowest toxicity is obtained when R_3 is a 2-methyl-1-butyl group. Of all the possible C_4 and C_5 alkyl groups, only the 2-methyl-1-butyl group is both primary and asymmetric, i.e., capable of existing as dextro and levo forms.

TABLE 6 BRONCHODILATION ACTIVITY OF 1,3,8-TRIALKYL-7-CARBOMETHOXYXANTHINES



CK	R_1	R_3	R_8	R_7	BD (*guinea pig*) mpK	30'	1h	2h	4h	6h	10h	AA (*rat*) mpK	1h	SP *in vitro* C
4274	CH_3	CH_2CHME_2	H	$COOCH_3$	15po	92	87	64	18			5ip	74	M/2000
					40po	lethal 1/6								
4380	CH_3	$CH_2CHMeEt$	H	$COOCH_3$	40po		99		57	12		5po	66	M/700
					20po		64							
4377*	CH_3	$CH_2CHMePr$	H	$COOCH_3$	80po		72		0					
					20po		64							
4378*	CH_3	CH_3	CH_3	$COOCH_3$	60po		96		95	89		75ip	54	M/10
4390	CH_3	CH_2CHMe_2	CH_3	$COOCH_3$								2ip	60	M/1000
					10po	49	86			79	48	4ip	52	
												2.5po	77	
4387	CH_3	$CH_2CHMeEt$	CH_3	$COOCH_3$	10po	44	87			59	37			M/1000
					20po		94			92		2.5po	72	
												5po	68	
												10po	57	
												5ip	55	
4477	CH_3	$CH_2CHMeEt$	CH_3	$COOC_2H_5$	10po	47	87			50				
4488	CH_3	$CH_2CHMeEt$	CH_3	$COOC_3H_7(n)$	10po		24			44				
					20po		78			68				
					40po		100			89				
					80po	lethal 1/4								

TABLE 6 (Continued)



CK	R_1	R_3	R_6	R_7	BD (*guinea pig*) mpK	30′	1h	2h	4h	6h	8h	AA (*rat*) mpK	1h	SP *in vitro* C
4491	CH_3	CH_2CHEt | Me	C_2H_5	$COOCH_3$	10po		25			21				
					40po		52							
4494	C_2H_5	CH_2CHEt | Me	CH_3	$COOCH_3$	10po		0			49				
					40po		9			80				
					80po	lethal 2/2								
4498	C_2H_5	CH_2CHEt | Me	C_2H_5	$COOCH_3$	40po		15			38				
					80po		63			79				
4507	CH_3	$CH_2(CH_2)_3Me$	CH_3	$COOCH_3$	10po		26			–				
					20po		52			–				
					40po		100			63				
					80po	lethal 2/2								
4505	CH_3	CH_2CH_2CHMe | Me	CH_3	$COOCH_3$	10po					15				
					40po		–			–				
					80po	lethal 3/5								
4515*	CH_3	CH_2CHCH_2Et | Me	CH_3	$COOCH_3$	20po		7			–				
					40po		100			–				
4373*	CH_3	$CH_2CHMePr$	CH_3	H	40po		71		87	96		20ip	54	M. 20
					80po		81		100					

* for comparison.

* for comparison.

Example 9.

This Example illustrates the antiallergy properties of the compounds of this invention.

1,8 - Dimethyl - 3 - (2 - methyl - 1 - butyl) - 7 - carbomethoxyxanthine, 1,8-dimethyl - 3 - isobutyl - 7 - carbomethoxyxanthine and 1,8 - dimethyl - 3 - (2-methyl - 1 - butyl)xanthine were tested in the rat passive cutaneous anaphylaxis screen described above.

The data in Table 6 shows that these compounds are effective antiallergy agents.

TABLE 7 PERCENT PROTECTION IN THE RAT PASSIVE CUTANEOUS ANAPHYLAXIS SCREEN

No.	Compound	Dose (mg/kg) & Route	Wheel Diameter (cm): Mean ± S.E.M.			Wheal Intensity: Mean ± S.E.M.		
			Control	Response	% Δ	Control	Response	% Δ
4387	1,8-dimethyl-3-(2-methyl-1-butyl)-7-carbomethoxyxanthine	10po	2.39 ± 0.10	1.41 ± 0.17	41	2.46 ± 0.13	1.65 ± 0.20	33
		20po	1.90 ± 0.15	0.81 ± 0.13	57	1.91 ± 0.21	1.18 ± 0.21	38
4380	1,8-dimethyl-3-isobutyl-7-carbomethoxyxanthine	20po	1.86 ± 0.15	0.74 ± 0.21	60	2.35 ± 0.21	1.10 ± 0.23	53
4383	1,8-dimethyl-3-(2-methyl-1-butyl) xanthine	20po	1.50 ± 0.16	0.74 ± 0.16	50	2.17 ± 0.21	1.13 ± 0.27	48

Example 10.

This Example illustrates the effectiveness of the compounds of this invention in the dog.

The results of studies at cardiopulmonary activity in the dog by the above described procedures are shown in Table 8. The data show that compounds 4390, 4387, and 4383 significantly reduce the decrease in pulmonary compliance and increase in pulmonary resistance due to histamine administration. The corresponding values for theophylline, a clinically used xanthine bronchodilator, are shown for comparison. It can be seen that the three compounds of this invention are more potent bronchodilators than theophylline in the dog.

TABLE 8: CARDIOPULMONARY ACTIVITY IN THE DOG

	CP (dog) (mean value at 2h)					
	mpK	BP	HR	PC	PR	RMV
4387	1po	↓17	↑40	↑40	↓61	↑39
	2po	↓03	↑16	↑60	↓85	↑10
	3po	↓08	↑08	↑74	↓100	↑68
	4po	↓25	↑17	↑42	↓77	↑76
4390	3po	↓07	↑13	↑70	↓85	↑41
Theophylline	40po	↓08	↑06	↑25	↓36	↑38
4383	1po	↓12	↑21	↑18	↓36	↑33

Example 11.

Tablets

19.5 grams of starch are dried to a moisture content of 10%. 0.5 grams of 1,8-dimethyl-3-(2-methyl-1-butyl)-7-carbomethoxyxanthine in finely powdered form are thoroughly mixed with the starch. The mixture is compressed into slugs. The slugs are reground into powder of 14—16 mesh size. This powder is recompressed into tablets weighing 200 mg. each. Each tablet thus has the composition:

1,8-dimethyl-3-(2-methyl-1-butyl)-7-carbomethoxyxanthine	5 mg
Starch	195 mg

Examples 12.

Capsules

A dry mixture of 19.5 grams of starch and 0.5 grams of 1,8-dimethyl-3-(2-methyl-1-butyl)-7-carbomethoxyxanthine is prepared as described in Example 11. The powder is loaded into hard gelatin capsules that each capsule contains 200 mg of the powder.

Example 13.

Sublingual Tablets

Tablets for sublingual administration were prepared by standard procedure, each tablet containing 5 mg of 1,8-dimethyl-3-(2-methyl-1-butyl)-7-carbomethoxyxanthine in a rapidly disintegrating base comprising starch, lactose, sodium saccharin and talcum.

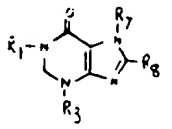
Example 14.

Aerosol

Five grams of 1,8-dimethyl-3-(2-methyl-1-butyl)-7-carbomethoxyxanthine were dissolved in 1000 grams of a mixture of 20 parts by weight of dichlorodifluoromethane and 80 parts by weight of 1,2-dichloro-1,1,2,2-tetrafluoroethane and loaded into a conventional aerosol medication dispenser to provide a means of administering the active ingredient by inhalation.

WHAT WE CLAIM IS:—

1. A compound having the formula:—



wherein:

$R_1 = C_1$—C_2 alkyl;

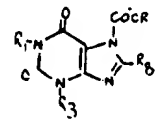
$R_3 = $—$CH_2$—($C_3$—$C_4$) alkyl or —$CH_2$—($C_3$—$C_4$ cycloalkyl);

R_7 = H or COOR in which R = C_1—C_4 alkyl, 2-halo C_2—C_3 alkyl or phenyl; and

R_8 = H or C_1—C_4 alkyl,

provided that R_7 and R_8 are not H simultaneously

2. A compound according to Claim 1 and having the general formula:—



wherein:

$R_1 = C_1$—C_2 alkyl,

$R_3 = CH_2$—(C_3—C_4 alkyl),

CH_2—(C_3—C_4)—cycloalkyl,

R_6 = H, C_1—C_2 alkyl,

R = C_1—C_4 alkyl, 2-halo-(C_2—C_3 alkyl), or phenyl.

3. A compound according to Claim 2 wherein R_1 = methyl.

4. A compound according to Claim 2 wherein R_3 is n-butyl.

5. A compound according to Claim 2 wherein R_3 is isobutyl.

6. A compound according to Claim 2 wherein R_3 is n-pentyl.

7. A compound according to Claim 2 wherein R_3 is isopentyl.

8. A compound according to Claim 2 wherein R_3 is 2-methyl-1-butyl.

9. A compound according to Claim 2 wherein R_3 is cyclopropylmethyl.

10. A compound according to Claim 2 wherein R_3 is cyclobutylmethyl.

11. A compound according to Claim 2 wherein R_6 is ethyl.

12. A compound according to Claim 2 wherein R_6 is methyl.

13. A compound according to Claim wherein R is ethyl.

14. A compound according to Claim 2 wherein R is methyl.

15. 1,8-Dimethyl-3-(2-methyl-1-butyl)-7-carbomethoxyxanthine.

16. *dextro*-1,8-dimethyl-3-(2-methyl-1-butyl)-7-carbomethoxyxanthine.

17. *levo*-1,8-dimethyl-3-(2-methyl-1-butyl)-7-carbomethoxyxanthine.

18. 1,8-Dimethyl-3-(2-methyl-1-butyl)-7-carboethoxyxanthine.

19. *dextro*-1,8-dimethyl-3-(2-methyl-1-butyl)-7-carboethoxyxanthine.

20. *levo*-1,8-dimethyl-3-(2-methyl-1-butyl)-7-carboethoxyxanthine.

21. 1,8-Dimethyl-3-(2-methyl-1-butyl)-7-carbopropoxyxanthine.

22. 1-Methyl-3-(2-methyl-1-butyl)-7-carbomethoxyxanthine.

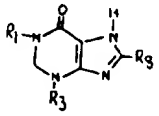
23. *dextro*-1-Methyl-3-(2-methyl-1-butyl)-7-carbomethoxyxanthine.

24. *levo*-1-Methyl-3-(2-methyl-1-butyl)-7-carbomethoxyxanthine.

25. 1,8-Dimethyl-3-isobutyl-7-carbomethoxyxanthine.

26. 1,8-Dimethyl-3-isobutyl-7-carboethoxyxanthine.

27. A compound according to Claim 1 and having the general formula: —



wherein:

R_1 = methyl,

$R_3 = CH_2$—(C_3—C_4 alkyl),

—CH_2—(C_3—C_4)—cycloalkyl, and

$R_8 = C_1$—C_2 alkyl.

28. A compound according to Claim 27 wherein R_3 is isobutyl or 2-methyl-1-butyl.

29. A compound according to Claim 27 wherein R_3 is n-butyl.

30. A compound according to Claim 27 wherein R_3 is isobutyl.

31. A compound according to Claim 27 wherein R_3 is n-pentyl.

32. A compound according to Claim 27 wherein R_3 is isopentyl.

33. A compound according to Claim 27 wherein R_3 is 2-methyl-1-butyl.

34. A compound according to Claim 27 wherein R_3 is cyclopropylmethyl.

35. A compound according to Claim 27 wherein R_3 is cyclobutylmethyl.

36. A compound according to Claim 27 wherein R_4 is ethyl.
37. A compound according to Claim 27 wherein R_4 is methyl.
38. 1,8-Dimethyl-3-(2-methyl-1-butyl)xanthine.
39. *dextro*-1,8-dimethyl-3-(2-methyl-1-butyl)xanthine.
40. *levo*-1,8-dimethyl-3-(2-methyl-1-butyl)xanthine.
41. 1,8-Dimethyl-3-isobutylxanthine.
42. A process for preparing a compound as claimed in Claim 1 in which R_7 is COOR, which process comprises reacting a sodium salt of a 1,3-dialkyl- or 1,3,8-trialkylxanthine in which the 1-alkyl group is as defined for R_1 in Claim 1, the 3-alkyl group is as defined for R_3 in Claim 1 and the 8-alkyl group is as defined for R_4 in Claim 1, with an alkyl chloroformate of formula ClCOOR in which R is as defined in Claim 1.
43. A process as claimed in Claim 42 and substantially as hereinbefore described in Example 3 or Example 4.
44. A process for preparing a compound as claimed in Claim 1 in which R_7 is hydrogen which process comprises cyclizing a 4 - amino - 5 - alkanoylamino - 1,3-dialkyluracil in which the 1-alkyl group is as defined for R_1 in Claim 1, the 3-alkyl group is as defined for R_3 in Claim 1 and the alkanoylamino group is of formula $-NHCOR_8$ in which R_8 is as defined in Claim 1.
45. A process as claimed in Claim 44 and substantially as hereinbefore described in Example 2.
46. A compound as claimed in Claim 1 and obtained by a process as claimed in any one of Claims 42 to 45.
47. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective for bronchodilation in combination with a pharmaceutically acceptable carrier.
48. A composition according to Claim 47 in the form of a tablet.
49. A composition according to Claim 47 which is in the form of a capsule containing a compound as claimed in Claim 1 optionally in the form of a mixture thereof with a pharmaceutical carrier material.
50. A composition according to Claim 47 in the form of a sublingual tablet.
51. A composition according to Claim 47 wherein said diluent is an aerosol propellent.
52. A composition according to Claim 47 comprising 1,8 - dimethyl - 3 - (2-methyl - 1 - butyl) - 7 - carbomethoxyxanthine dissolved in a pharmaceutically acceptable aerosol propellant.
53. A composition according to Claim 47 comprising 1,8 - dimethyl - 3 - (2-methyl - 1 - butyl)xanthine dissolved in a pharmaceutically acceptable aerosol propellant.
54. A pharmaceutical composition in the form of a tablet comprising between 2 mg and 50 mg of a compound according to Claim 2 in combination with non-toxic pharmaceutically acceptable excipients.
55. A pharmaceutical composition in the form of a tablet comprising between 1 mg and 100 mg of a compound according to Claim 27 in combination with non-toxic pharmaceutically acceptable excipients.
56. A compound according to Claim 1 and specifically identified herein.
57. A pharmaceutical composition substantially as described in any one of Examples 11 to 14.

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